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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/592,919	07/31/2007	Michael T. Migawa	CORE0037USA	2825

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
11/25/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/592,919	MIGAWA ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/10/11*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,11-17,19-22,24 and 26-32* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 9, 11-13, 17, 19-22, 24, 26-28, and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 11/10/11 has been considered.

It is noted that applicant elected modified nucleotide, more specifically, modified base nucleotide, more specifically tetrafluoroindolyl, without traverse in the reply filed on 8/17/10.

This application contains claims 14-46 and 29-31 that is drawn to an invention nonelected **without traverse** in the reply filed on 8/17/10. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9, 11-13, 17, 19-22, 24, 26-28, and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification does not describe the instantly claimed genus of transition moieties in a manner that would allow the skilled artisan to envision which

moieties would in fact modulate the transmission of the conformation of the second region to the first region. The specification does not set forth any structural criteria to allow one to envision the genus of molecules that would in fact act via the claimed mechanism.

Furthermore, the specification does not set forth any structural criteria for modified bases to allow one to envision the genus of modified bases that do not form hydrogen bonds with the target RNA but optionally stack with adjacent bases.

Applicant argues that the specification describes the structural criteria at length. Although the specification sets forth examples, it does not define the genus as instantly claimed. The specification does not describe the genus of compounds that have a modified nucleotide transition moiety that does not form hydrogen bonds with the target and transitions the second region to the first region. The claim language is extremely broad and one would not be able to readily envision which modifications are necessarily included or excluded from the oligomer to result in the instant method.

The instant genus is undefined and the claims do not set forth any structural criteria to define which modifications are intended to fall within the instant genus. As recited in claim 9, any modified base that does not hydrogen bond meets the limitations of the base claim.

The claims embrace an undefined genus of modifications with no specific structure that would necessarily result in the instant outcome. The claims are not limited to the specific examples given in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 9, 11-13, 17, 19-22, 24, 26-28, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krotz et al. (US 2003/0096770 A1), in view of Lai et al. (J. Am. Chem. Soc. Vol. 126 No. 10 2004, published on-line 2/21/04).

Krotz et al. teach a method of modulating the expression of a target RNA comprising administering an antisense oligonucleotide specific for the target. Krotz et al. teach an oligonucleotide that has a first region of nucleotides of one conformation, which comprises deoxynucleotides, and a second region that is 5' to the first region that comprises 2'-O-methoxyethyl groups. Additionally, the oligo comprises phosphorothioate linkages. There is a transitional moiety between the 2'-O-methoxyethyl and deoxynucleotides that incorporates a 5-methylcytosine (see ISIS-9606, page 8, for example). Additionally, the oligonucleotide has a third region of the same type as the second region that again is separated from a deoxynucleotide by a 5-methylcytosine.

Krotz et al. teach "chimeras" may be "gapmers," i.e., oligonucleotides in which a central portion (the "gap") of the oligonucleotide serves as a substrate for, e.g., RNase H, and the 5' and 3' portions (the "wings") are modified in such a fashion so as to have greater affinity for, or stability when duplexed with, the target RNA molecule but are unable to support nuclease activity (e.g., 2'-fluoro- or 2'-methoxyethoxy-substituted).

Krotz et al. teaches that the compounds are administered to humans and human cells.

Additionally, Krotz et al. teach fluorinated oligonucleotides are preferred.

Krotz et al. do not teach tetrafluoroindolyl modifications.

Lai et al. that melting studies of DNA duplexes containing 4,5,6,7-tetrafluoroindole bases show greater stabilization of the duplex compared with nonfluorinated hydrocarbon controls. Overall, these hydrophobic analogues are destabilizing compared with natural base pairs but are stabilizing compared with natural base mismatches. Our findings suggest that polyfluoroaromatic bases might be employed as a new, selective base-pairing system orthogonal to the natural genetic system.

It would have been obvious to incorporate fluorinated nucleotides into the oligonucleotide of Krotz et al. set forth above since Krotz et al. teach modifications as preferred modifications to increase the binding affinity and enhance the overall activity of the oligonucleotide.

It would have been obvious to specifically incorporate tetrafluoroindolyl modifications given that Lai et al. teach the properties of such modifications and teach that these bases might be employed as a new, selective base-pairing system orthogonal to the natural genetic system.

The specific oligonucleotide set forth above incorporates a 5-methylcytosine between each of the regions. It would have been obvious to incorporate 2 of such modifications or 2 tetrafluoroindolyl modifications as a matter of design choice and would certainly be within the realm of routine optimization of the molecule.

Gapmer chemistry was well known in the art before the time of filing. One would have a reasonable expectation of success in combining the modifications and resulting in active molecules given that Krotz et al. teach that each of the modifications enhance the activity of antisense oligonucleotides and it was known that tetrafluoroindolyl modifications exhibit stabilization properties.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

The claims filed on 8/17/10 recited any modified base as the modification (claim 9) and any fluorinated base (claim 12). As drafted, these modifications would necessarily meet the limitations of the base claim if the claims are enabled.

The claims have now been amended and the base claim now requires that the modification of the transition region cannot bind to the target and the specific types of modifications depend from this claim limitation. As set forth in the written description rejection above, it is unclear what modifications in fact possess the characteristic that is now required by the base claim.

Applicant argues that the office has not provided a reason why one would incorporate the modifications taught by Lai with the oligonucleotides of Krotz because Lai teaches that the incorporation of fluorinated nucleosides destabilizes binding affinity. As set forth above, Lai et al. that melting studies of DNA duplexes containing 4,5,6,7-

tetrafluoroindole bases show greater stabilization of the duplex compared with nonfluorinated hydrocarbon controls.

Given that Krotz teaches gapmer chemistry for oligonucleotides and Lai teaches a specific modification that demonstrated greater stabilization, it would have been a matter of design choice to incorporate the modification of Lai into the oligomer of Krotz.

Krotz teaches various modifications that can be incorporated including 5-methyl cytosines or 5-trifluoromethyl modifications (see page 6).

Applicant argues that Lai teaches away from utilizing the specific modification for RNA binding. Simply because Lai et al. examined DNA affinity does not mean that the modification is taught away from with respect to RNA affinity. Lai offers sufficient motivation to incorporate this type of modification into a DNA oligomer.

It is noted that applicant's arguments are specific to tetrafluoroindolyl modifications, wherein fluorinated bases are only an element of claims 12, 13, 27, and 28. The remainder of the claims are considered obvious in view of Krotz et al. alone, who teaches gapmer chemistry and incorporation of a transition moiety.

Furthermore, the claims utilize open language and can therefore comprise additional elements/modifications.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Tuesday-Friday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on (571) 272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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